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Intraperitoneal Chemotherapy: historic anomaly or hope for the future?

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Introduction

Intraperitoneal (IP) chemotherapy for advanced ovarian cancer remains a controversial treatment option, with conflicting views amongst gynaecological and medical oncologists worldwide. The benefit of intraperitoneal chemotherapy has been described in multiple trials, notably the pivotal randomised controlled trial by Armstrong *et al.* published in the New England Journal of Medicine. (1) Shortly following this in 2006, the National Cancer Institute (NCI) released a statement promoting the use of intraperitoneal chemotherapy in women with advanced ovarian cancer. (2)

Despite this statement, the use of intraperitoneal chemotherapy has not been fully accepted or incorporated into current care. Concerns have been raised as to whether the findings from this trial truly have the weight to support intraperitoneal chemotherapy use as a standard of care. Toxicity associated with intraperitoneal administration is also a concern. Further questions have arisen regarding appropriate regimens, safe catheter administration, cost effectiveness and what patient subgroup are likely to have the best response.

Here, we firstly outline the rationale behind intraperitoneal administration. Thereafter, we outline previous phase III trials comparing intraperitoneal versus intravenous chemotherapy, in terms of efficacy and toxicity. We explore dosing and regimens, catheter technology, cost effectiveness and outline what subtypes are most likely to respond. Finally, we express our views as to whether intraperitoneal chemotherapy is a viable, safe and effective treatment for patients with advanced ovarian malignancy.

The rationale behind intraperitoneal chemotherapy

Epithelial ovarian cancer accounts for the majority of ovarian tumours and often presents at an advanced stage (III/IV). (3) Patients generally initially respond well to cytoreduction and combined platinum-taxane chemotherapy. However, ultimately the majority of patients experience disease relapse with a poor overall survival. Low residual disease volume in the pelvis is a well-established good prognostic indicator. (4)

In ovarian cancer, around 85% of patient have disease confined to the peritoneal cavity. (5) Cancer cells spread through this cavity, implanting on peritoneal surfaces and proliferating if the environment is neovascularly suitable. Spread may also be via the blood stream or lymphatic system, (6) although this is less common than in many other solid malignancies.

Given this natural history and the fact that the peritoneum is relatively accessible, intraperitoneal chemotherapy has been considered for decades. Pharmacokinetic advantages of intraperitoneal versus intravenous (IV) administration have been demonstrated in multiple studies. In intraperitoneal therapy, there are peak cytotoxic levels acting on peritoneal disease with an increased drug half-life, resulting in prolonged total drug exposure. (7) (8) Drugs administered into the peritoneal cavity are mainly taken up via the portal vein, and if they are hepatically metabolised may result in reduced systemic side effects. (8)

Despite these described benefits, intraperitoneal therapy may result in uneven drug distribution due to adhesions. There is also poor penetration into deeper areas of disease. (7) (9) This was demonstrated in animal models, where no difference in cytotoxic concentration was noted in the centre of tumours (any greater than 1-2mm from the surface) when comparing intravenous and intraperitoneal administration. (8) Overall, the ideal intraperitoneal agent would not require liver activation, have a slow rate of peritoneal clearance with the ability to penetrate deeply into peritoneal tumours. (8) Whether these described pharmacokinetic benefits can translate into improved clinical outcomes has been studied in phase III trials as outlined below.

Phase III trials comparing intraperitoneal versus intravenous chemotherapy: efficacy & toxicities

There have been many comparative trials of intraperitoneal versus intravenous chemotherapy in advanced ovarian malignancy. In the 1980s-1990s, multiple phase I and II trials identified intraperitoneal chemotherapy as a safe and feasible option, with unknown efficacy. (10-12)

There have been three large phase III trials which show superiority of intraperitoneal chemotherapy compared to intravenous. These are the trials by Alberts *et al.* 1996 (GOG-104), (13) Markman *et al.* 2001 (GOG-114) (14) and the GOG-172 trial by Armstrong *et al.* in 2006. (1) These studies randomised patients following primary debulking surgery. In addition, the OV21/PETROC study randomised patients who responded to neoadjuvant chemotherapy to either intravenous or intraperitoneal post-debulking chemotherapy. (15) This trial had to undergo a change in its design due to recruitment issues resulting in less power to show a difference between the treatment arms and the results can be regarded as equivocal. A number of trials have also failed to demonstrate superiority of intraperitoneal chemotherapy as detailed below. With the exception of the GOG-252 study, (16) which was unique in that bevacizumab was also given to patients in both arms, these negative studies have been underpowered.

Data showing superiority of intraperitoneal compared to intravenous chemotherapy:

Alberts et al. 1996 (GOG-104/SWOG-8501) conducted a phase III trial including 546 patients with stage III cancers (residual disease of less than 2cm). They received IV cyclophosphamide (600mg/m²) plus either, IP cisplatin (100mg/m²) or IV cisplatin (100mg/m²). (13) This was administered every 3 weeks, for a total of six cycles.

The median overall survival was significantly increased in the intraperitoneal cisplatin group versus intravenous cisplatin (49 months [CI 42-56], versus 41 months [CI 34-47]). The risk of death was lower in those treated with intraperitoneal chemotherapy, compared to intravenous (hazard ratio: 0.76 CI [0.61-0.96], p = 0.02). Subgroup analysis revealed those with low residual disease (less than 0.5cm) were more likely to respond. Abdominal pain (grade 2 or above) was higher in the intraperitoneal group, but this responded well to simple analgesics. Adverse effects such as neutropenia, tinnitus, hearing loss and neuromuscular effects were more frequent in the intravenous group, as opposed to the intraperitoneal group.(13)

This was the first trial to demonstrate superiority of intraperitoneal chemotherapy and the only variable factor was administration route (with the same chemotherapy and dosing in both arms). Despite these early promising results, the uptake of intraperitoneal chemotherapy did not significantly change amongst clinicians. This is likely because at the time of this publication there was emerging evidence to suggest the benefit of intravenous paclitaxel as combination first line therapy. The improved median survival when combining intravenous paclitaxel and intravenous platinum agents was significantly greater (14 months) than the substitution of intravenous cisplatin for intraperitoneal cisplatin (7 months). (13, 17)

Markman et al. (GOG-114/SWOG-9227) conducted a randomised trial in 426 patients with residual disease less than 1cm. (14) One treatment arm received the new standard of care which was IV paclitaxel (135mg/m²) over 24 hours, followed by IV cisplatin (75mg/m²), every 3 weeks for six cycles. The experimental treatment arm was IV carboplatin (AUC9) every 4 weeks for 2 cycles, then IV paclitaxel (135mg/m²) over 24 hours, followed by IP cisplatin (100mg/m²) every 3 weeks, for 6 cycles (total 8 cycles of chemotherapy). The initial intensive carboplatin aimed to minimise residual disease volume prior to intraperitoneal therapy.

Progression free survival (PFS) was significantly prolonged in the intraperitoneal group (28 versus 22 months, relative risk 0.78; p=0.01). Effect on overall survival (OS) was borderline

significant (median 63 versus 52 months, relative risk 0.81; $p=0.05$). There was a greater incidence of grade 3 toxicities (haematological, gastrointestinal and metabolic) in the intraperitoneal group. Therefore, 18% of patients received two or fewer cycles of intraperitoneal therapy. The beneficial effects of the experimental arm may be related to the greater number of cycles (8 versus 6), intensive carboplatin or higher dose of cisplatin. (18) Given the minimal effect on survival and considerable toxicities, the authors concluded the experimental arm was not recommended for routine practice. (14)

The GOG-172 phase III trial, published in 2006 included 429 patients with stage III ovarian cancer with residual disease of less than 1.0cm. (1) The experimental arm were given IV paclitaxel (135mg/m²), IP cisplatin (100mg/m²) and day 8 IP paclitaxel (60mg/m²). The control arm received IV paclitaxel (135mg/m²) and IV cisplatin (75mg/m²). Administration was three-weekly, for a total of six cycles. Primary outcomes were progression free survival (PFS) and overall survival (OS). Secondary endpoints included toxicities and quality of life.

There was a significant benefit in PFS in the intraperitoneal group (23.8 versus 18.3 months, relative risk 0.80 [0.64-1.00] $p=0.05$). However, the benefit of intraperitoneal therapy on overall survival was notably more significant than PFS (65.6 versus 49.7 months, relative risk 0.75 [0.58-0.97] $p=0.03$). (1) This overall survival benefit (15.9 months) was the greatest to date from a first line randomised controlled trial. (19) This survival benefit was present (although not statistically significant) on subgroup analysis in both those with residual and microscopic disease (relative risk 0.77 [0.57-1.04], 0.69 [0.41-1.17] respectively). (1)

The side effects and toxicities in the intraperitoneal group were significantly higher. Only 42% in the intraperitoneal group received six cycles, versus 83% in the intravenous group. Despite this, the majority (90% intravenous, 83% intraperitoneal) received six courses of some chemotherapy. Catheter-related complications ($n=40$, 33%) and toxicity ($n=31$, 26%) accounted for the majority of reasons for discontinuation of intraperitoneal therapy. (1)

Quality of life (QOL) was reported as poorer in the intraperitoneal group before cycle 4 and 3-6 weeks following treatment completion. However, no difference in QOL was present one year after treatment completion. (1) Shortly following this publication, the National Cancer Institute released a statement promoting the use of intraperitoneal chemotherapy, as described below.

The recently published OV21/PETROC study compared the use of intraperitoneal versus intravenous chemotherapy in 275 patients who had responded to neoadjuvant platinum based chemotherapy for stage IIB-IVA epithelial ovarian cancer and been successfully debulked to a

maximum residual disease of <1cm. The trial was designed so that the dose intensities were comparable between the intravenous and intraperitoneal arms. It started as a three-arm study comparing: paclitaxel 135mg/m² IV and carboplatin AUC 5/6 IV day1 plus paclitaxel 60mg/m² IV day8 versus; paclitaxel 135 mg/m² IV and cisplatin 75 mg/m² IP day1 plus paclitaxel 60 mg/m² IP day8 versus; paclitaxel 135 mg/m² IV and carboplatin AUC 5/6 IP day1 plus paclitaxel 60 mg/m² IP day8. After stage one of the study as the cisplatin IP arm had failed to show superiority, phase two proceeded as a direct comparison of the carboplatin IV versus IP arms. The primary endpoint was adjusted to 9-month progressive disease rate because of slow recruitment and lack of funding to proceed to the planned phase III recruitment of >800 patients. Using this endpoint, there appeared to be an advantage for the IP arm with 24.5% of patients having progressed at 9 months compared to 38.6% of the control arm, although this did not reach conventional levels of statistical significance (p=0.065). Importantly, the IP carboplatin regime was well tolerated with no difference in quality of life or toxicity when compared to the intravenous arm.

Data showing no survival benefit of intraperitoneal chemotherapy:

Kirmani et al. 1994, compared IV cisplatin (100mg/m²) and IV cyclophosphamide (600mg/m²) (3 weekly, 6 cycles), versus IP cisplatin (200mg/m²) and IP etoposide (350mg/m²) (4 weekly, 6 cycles), in 62 patients with stage IIC-IV disease. There was no difference in survival or in toxicities. (20)

Following the GOG-104 trial, a similar trial by Polyzos et al. (1999) analysed 90 patients with stage III disease. (21) They were randomised to either IV carboplatin (350mg/m²) plus IV cyclophosphamide (600mg/m²) (six cycles) or IP carboplatin (350mg/m²) plus IV cyclophosphamide (600mg/m²) (six cycles). Progression free survival was similar in both groups (19 months IV, 18 months IP), as was overall survival (25 months IV, 26 months IP). The intravenous group had higher rates of haematological toxicities. Authors concluded that intravenous and intraperitoneal carboplatin were equally effective, with less myelotoxicity with intraperitoneal administration. In comparison to GOG-104, this study was smaller and included variable residual disease. The findings suggested it was unlikely that patients with large residual disease benefit from intraperitoneal administration, compared to intravenous. This is consistent with findings from radiolabelled drug studies showing poor tumour penetration in larger tumours. (22)

Gadducci *et al.* 2000 analysed 113 patients with debulked stage II-IV ovarian tumours. (23) They were randomised to ipPEC; IP cisplatin (50mg/m²) plus IV epidoxuribicin (60mg/m²) and IV cyclophosphamide (600mg/m²), or ivPEC; IV cisplatin (50mg/m²) plus IV epidoxuribicin (60mg/m²) and IV cyclophosphamide (600mg/m²), given four weekly for 6 cycles. Treatment protocol changed in 2 patients in the ivPEC and 20 in the ipPEC group. There was a slight, but not statistically significant, difference in median PFS (42 months ipPEC versus 25 months ivPEC, $p=0.13$) and overall survival (67 months ipPEC and 51 month ivPEC, $p=0.14$). There was no significant difference in toxicities.(23)

Yen *et al.* 2001, compared 132 patients with minimal residual disease (less than 1cm) following cytoreduction. (24) Participants were randomised to either IP cisplatin (100mg/m²) or IV cisplatin (50mg/m²), along with IV cyclophosphamide (500mg/m²) and adriamycin or epirubicin. No difference in overall survival was noted. Frequency of haematological toxic effects was significantly reduced in the intraperitoneal group.

Although published in abstract form only to date, the GOG-252 study is important as it is the largest phase III study performed in the field and the only one to report results in the last decade. (16) This study enrolled 1560 participants with stage II-IV epithelial ovarian cancer in the first line post-operative setting. Patients were randomised to receive: IV carboplatin AUC6 three-weekly plus IV paclitaxel 80mg/m² weekly versus; IP carboplatin AUC6 three-weekly plus IV paclitaxel 80mg/m² weekly versus; IV paclitaxel 135mg/m² day1 plus IP cisplatin 75mg/m² day2 plus IP paclitaxel 80mg/m² day8 as part of a three-weekly regime. All patients also received IV bevacizumab 15mg/kg three weekly from cycle 2 to 22. There was no significant difference in PFS (median 24.9 months in IV arm versus 27.3 months in the IP carboplatin arm and 26.0 months in the IP cisplatin arm). It has been suggested that including bevacizumab or weekly treatment in each arm may have negated the impact of intraperitoneal chemotherapy in this study. It is also of note that the dose of IP cisplatin (75mg/m²) used was less than the 100mg/m² used in all of the positive studies to date.

Consolidation therapy:

Piccart *et al.* 2003, uniquely analysed 153 patients with mainly stage III ovarian cancer who had achieved pathological complete remission following intravenous chemotherapy and cytoreduction. They were randomised to 4 cycles of intraperitoneal cisplatin (90mg/m² every 3 weeks) or observation. Following 8 years of follow up, the hazard ratios for PFS and OS were 0.89 (95% CI: 0.59-1.33) and 0.82 (0.52-1.29). This suggested a slight treatment benefit but

not substantial enough to support a change in clinical practice. (25) Interestingly, a Cochrane review found no evidence to suggest intravenous maintenance chemotherapy improved survival, versus observation. Therefore, the lack of benefit in this trial is likely not solely related to route of administration. (26)

National Cancer Institute Announcement:

In 2006, following the GOG-172 trial, the National Cancer Institute (NCI) issued a statement. Following data analysis, they concluded intraperitoneal therapy was associated with an average 21.6% reduction in risk of death (HR 0.79 [0.70=0.89]). This clinically translated to a 12 month increase in overall survival (based on expected median survival 4 years). Their announcement encouraged the use of intraperitoneal chemotherapy in women following optimal cytoreduction, stating “*strong consideration should be given to a regimen with intraperitoneal cisplatin and a taxane, whether given by an IV only or IV plus IP*”. (2) Extensive adhesions was a relative contra-indication due to poor drug distribution. (7) They acknowledged the greatest survival benefit was observed with IP cisplatin 100mg/m², though the optimal intraperitoneal regimen was unclear. Toxicities were acknowledged but felt to be short-term and treatable.

Following this announcement, there was significant disagreement between clinicians worldwide. Gore et al. 2006 published a commentary outlining multiple reasons why they felt the GOG-172 trial did not support intraperitoneal chemotherapy as standard care. (27) They meticulously analysed study design, stated the benefit was statistically marginal, raised concerns as to whether it was truly intention to treat (14 patients not included in survival calculation), and questioned how patients lost to follow up would affect results. They questioned whether a minimal improvement in PFS with a notable improvement in overall survival, was due to treatments following relapse or the intraperitoneal chemotherapy itself. No data detailing patient treatment following relapse was available. Whether intraperitoneal chemotherapy changes tumour biology and affects response to subsequent therapies remains unknown. (8) The use of intravenous cisplatin as the GOG-172 control arm was also criticised. Though no statistical significance between intravenous cisplatin and intravenous carboplatin was demonstrated in the GOG-158 trial, there was a trend towards superiority of intravenous

carboplatin. (28) The improved outcome of the intraperitoneal treatment arm in GOG-172 was speculated to be heightened by using intravenous cisplatin, which is not the current standard of care. (5) Armstrong responded, justifying their study design, acknowledging toxicity concerns but overall continued to strongly support intraperitoneal chemotherapy. (29) Interestingly, a Cochrane systematic review still identified a survival benefit when GOG-172 and GOG-114 were removed from analysis. (9)

Following the NCI announcement, the Society of Gynaecology Oncologists also released a supportive statement, but they reiterated intraperitoneal chemotherapy should only be for patients optimally debulked and initiated by clinicians with expertise in catheter technology. (30)

Systematic Review:

A Cochrane systematic review based on 8 clinical trials (2026 patients) identified a significant improvement in overall survival (HR 0.81, 95% CI: [0.72-0.90]) in those treated with intraperitoneal versus intravenous chemotherapy. A significant progression free survival benefit (HR 0.98, 95% CI: [0.70-0.86]) was also identified.(9) Data was homogenous with no significant difference between subgroups.

The authors concluded that intraperitoneal chemotherapy provided a survival advantage, but with increasing toxicities. They identified the importance of an individualised approach to each patient and further investigation into optimal dosing and administration. (9)

Toxicities:

Of the three positive trials, GOG-104 reported reduced toxicities in the intraperitoneal chemotherapy group. (13) However, both GOG-114 and GOG-172 reported increased toxicities, which resulted in a significant proportion not completing intended intraperitoneal cycles. (1) (14) In Cochrane review, those treated with intraperitoneal chemotherapy were more likely to suffer adverse effects, notably; pain, fever, infection, metabolic and gastrointestinal toxicities. The data was heterogeneous and analysis less reliable. (9)

Adverse effects can be categorised into chemotherapy-related or catheter-related. There was insufficient data for the Cochrane review to analyse catheter-related complications. (9) GOG-172 reported catheter-related complications in around 33% of patients. Catheter type and timing were not specified in study design. Thirty six percent of patients not completing assigned intraperitoneal therapy was due to catheter complications, mainly infection or failure. Interestingly, patients with previous left colonic or recto-sigmoidal resection were less likely to receive planned intraperitoneal chemotherapy due to complications. (1)

The NCI recommended a semi-permanent subcutaneous venous access port connected to a single lumen venous catheter. Fenestrated catheter designs were discouraged, due to increased rates of bowel complications. (2) A retrospective study of 301 patients analysed complications of subcutaneous catheters. Catheters were often placed at laparotomy (69.6%) and otherwise were inserted at laparoscopy (19.5%) or as a separate procedure (10.9%). Only 30 women (10%) experienced complications, notably infection and obstruction. Only 21 patients (7%) had to stop intraperitoneal chemotherapy early. No incidents of bowel perforation or obstruction occurred. Higher rates of malfunction and infection were noted if catheter placement was during laparotomy. Therefore, toxicity may be minimised by instead placing catheters at laparoscopy. (31)

Haematological chemotherapy-related toxicities were higher in the intraperitoneal group in GOG-172 (leucopenia $p < 0.001$, thrombocytopenia $p = 0.002$). This resulted in delay or omission of day 8 chemotherapy. (1) Neurotoxicity was also significantly higher in the intraperitoneal group ($p = 0.001$). This may be due to dosing, as opposed to administration. Alberts *et al.*, who used the same intravenous and intraperitoneal dose of cisplatin, conversely showed decreased neurotoxicity in the intraperitoneal group. (13) Neurotoxicity is especially important as further analysis of GOG-172 showed these toxicities are not necessarily treatable or short lived. (32)

The reported high incidence of toxicities has resulted in reluctance to incorporate intraperitoneal therapy into standard care. Catheter-related toxicities may be significantly minimised with appropriate catheter training and timing of insertion. Chemotherapy-related toxicities may be minimised by altering regimens or dosing.

Regimens & Dosing:

Many cytotoxic agents have been tested via the intraperitoneal route. Intraperitoneal cisplatin has been extensively investigated, at doses between 50mg/m² to 200mg/m². Cisplatin plasma levels are lower when the drug is administered into the peritoneum as opposed to intravenously, which may reduce systemic toxicities. Intraperitoneal cisplatin has a 10-20 fold increased peritoneal exposure compared to intravenous. (10) It has been argued that the high dose of 100mg/m² (as used in GOG-172) may not be necessary, as a dose reduction would still allow at least 10 times the concentration of systemic cisplatin to be delivered directly to the peritoneum. Reduced dose may result in reduced systemic toxicity. (33) However, it is also notable that all the positive studies (GOG-104, GOG-114 and GOG-172) used IP cisplatin at a dose of 100mg/m², whereas the only adequately powered negative study (GOG252) used IP cisplatin at a dose of 75mg/m².

Carboplatin is equally as effective as cisplatin as an intravenous therapy, with reduced toxicities. (28) Intraperitoneal carboplatin has been investigated, but significantly less than cisplatin. This is likely due to early animal data, which demonstrated that 10 times the dose of intraperitoneal carboplatin was required for the equivalent dose of intraperitoneal cisplatin. (34) Retrospective analysis of patients treated with intraperitoneal cisplatin or carboplatin showed poorer response rates in those given carboplatin. (35) However, emerging retrospective data indicates around 400mg/m² of intraperitoneal carboplatin is required for a survival benefit. This dose is considerably more than what was investigated in the previous negative trials (200-300mg/m²), which may have resulted in falsely poor results. Intraperitoneal carboplatin is an effective, tolerable second line therapy in patient with minimal residual disease following intravenous cisplatin at a dose between 150-300mg/m². (36, 37) This emerging evidence, along with the reduced neurotoxicity compared to a cisplatin paclitaxel combination, has led to increased interest in intraperitoneal carboplatin. (8) (38)

Intraperitoneal paclitaxel is poorly absorbed into the peritoneum, resulting in cytotoxic concentrations for 24-48 hours following administration. (39) It can penetrate effectively through 80 cell layers. (8) Phase I and II trials found dosing of 60-75mg/m² was effective and safe, with severe abdominal pain causing dose limiting toxicity. (8, 39, 40) (41) (42) Whether a taxane component should be given intra-peritoneal is debatable and could not be established in the Cochrane meta-analysis. (9)

Observational results of a new standardized protocol for intraperitoneal therapy in 69 patients with stage IIC-IV disease (residual <1cm) was reported. The protocol was; day 1 IV paclitaxel 135mg/m², day 2 IP cisplatin 75mg/m², day 8 IP paclitaxel 60mg/m², three-weekly for six cycles. (43) It included a standardised list of supportive medications, such as routine use of GCSF. Overall, patients received a greater number of intraperitoneal cycles compared to GOG-172 (4.28 versus 3.66, $p = 0.0088$). There was a decreased rate of adverse events, including reduced neutropenia (48% versus 76%) and infection (5% versus 16%). The effect on survival was not analysed. (43) Furthermore, an outpatient-based regimen with a lower dose of cisplatin has been suggested: IV paclitaxel (135 mg/m²) over 3 hours on day 1, IP cisplatin (75 mg/m²) on day 2, and IP paclitaxel (60 mg/m²) on day 8, given every 21 days for 6 cycles. Median PFS was 29 months and overall survival 67 months, which was similar to GOG-172. A higher proportion completed treatment (80% completing 4 or more cycles, 56% completing all 6 cycles). (44) Both these observational studies suggest alterations in dosing and setting may still have potential survival benefits, whilst improving tolerability, although a randomised study would be required to demonstrate this.

The optimum number of cycles is controversial. Analysis of 367 patients with stage III ovarian cancer followed up for 7 years suggested at least 5 cycles were needed for a survival advantage. (45) Longer term survival was analysed using participants from GOG-114 and GOG-172, with median follow up of 10.7 years. Median survival was prolonged in the intraperitoneal group (61.8 months versus 51.4 months). The risk of death was decreased by 12% for each cycle of intraperitoneal chemotherapy completed (AHR 0.88 95% CI 0.83-0.94 $p<0.001$). (46) Conversely, another analysis of 201 patients observed over 6 years illustrated no survival difference at 5 years between patients who received 1 to 2, 3 to 4, 5 to 6 cycles of intraperitoneal chemotherapy. (47) Overall, completion of intraperitoneal cycles appears to have pronounced effects, especially on long term outcome, and therefore ways to improve tolerability are paramount.

Cost Effectiveness:

In 2007, Bristow *et al.* performed a cost-effectiveness analysis comparing intraperitoneal cisplatin and paclitaxel versus intravenous carboplatin and paclitaxel, utilising GOG-172 and GOG-158 data. Intraperitoneal chemotherapy had an overall high cost of \$39,861 per patient with an effectiveness of 5.16 QALYs. In comparison, intravenous therapy was \$18,822 per patient with 4.59 QALYs. Inpatient treatment accounted for 43.2% of intraperitoneal chemotherapy cost, due to inpatient administration and toxicity related hospitalization. Though intraperitoneal therapy was cost-effective, minimising administration costs would benefit overall treatment value.(48)

Havrilesky *et al.* 2008 similarly used the GOG-172 and GOG-158 data to assess cost effectiveness. Utilising a different model, they included costs for treatment and supportive care, and compared cost effectiveness of intravenous versus intraperitoneal therapy at 7, 11.5 and 35 year horizons. Analysis included intravenous carboplatin/paclitaxel, intravenous cisplatin/paclitaxel and intraperitoneal cisplatin/paclitaxel. The incremental cost effectiveness ratio (ICER) was estimated at around \$180,022 at the 7 year horizon, significantly more than Bristow *et al.* prediction (ICER \$37,454). (49) (48)

This discrepancy is likely due to; utilising different models with trial data at 6 month intervals, using mean survival time (as opposed to median) and estimating costings on intended as opposed to completed treatments. Similarly to Bristow, Havrilesky attributed the majority of cost to inpatient administration. Intraperitoneal cisplatin/paclitaxel administered as an outpatient would have favourable ICER to equivalent intravenous therapy. This relies on assumption that a shorter administration of intraperitoneal paclitaxel is equally as effective. Intraperitoneal treatment became more cost effective when a longer time horizon was modelled, providing the survival benefit persists. (49)

Both studies highlight intraperitoneal chemotherapy is expensive. Any attempts to reduce costs via using outpatient administration and reduce toxicity related hospitalization are key.

Subtypes:

Identifying patient who are more likely to have a good response to intraperitoneal chemotherapy would allow a tailored treatment approach. Those with low volume residual disease are more likely to respond to intraperitoneal chemotherapy as described. (13) Previous colonic resection has been associated with treatment non-completion due to complications and is a relative contra-indication. (1) (9) (45) Upper abdominal tumour metastasis was also associated with increased likelihood of discontinuing treatment. (45) The prognosis in elderly patients with clear cell tumours is poor and toxicities from intraperitoneal therapy are likely to exceed potential benefit according to Cochrane review. (45) (9)

BRCA1 status, by immunohistochemistry, was examined in GOG-172 participants. Deleterious *BRCA1* gene mutations whether derived from the germline or somatically acquired result in loss of protein expression. Previous data suggests reduced BRCA1 expression is associated with platinum hypersensitivity.(50) Of the 393 patients analysed, 189 patients had reduced or absent BRCA1 expression and 204 had normal expression. Interestingly, in those with abnormal BRCA1 expression the overall survival was significantly increased in the intraperitoneal group, versus intravenous group (84 versus 47 months, $p = 0.0002$). Abnormal BRCA expression was an independent prognostic factor for improved survival in the intraperitoneal group (HR 0.67 [0.47- 0.97], $p = 0.032$). In those with normal BRCA1 expression, survival was similar when comparing intravenous versus intraperitoneal therapy. (51) These findings raise the possibility that patients with deleterious *BRCA1* mutations, which are known to confer increased platinum sensitivity, particularly benefit from the increased dose intensity resulting from the intraperitoneal route of administration.

Polymorphisms in the excision repair cross complementation group 1 (ERCC1) were investigated using GOG-172 data. The C8092A polymorphism was identified as a predictor of survival. Unfortunately, numbers were insufficient to make accurate conclusions to whether administration route influenced this, though this association was more pronounced in the intraperitoneal treatment arm. (52)

Uptake of intraperitoneal chemotherapy:

Despite the described trials and the NCI alert, the uptake of intraperitoneal chemotherapy has been poor. The clinical use of intraperitoneal therapy was analysed using a prospective cohort study of over 800 woman with stage III debulked ovarian tumours from 6 National Comprehensive Cancer Network Institutes between 2006 and 2012. Intraperitoneal chemotherapy use increased from 0% to 33% between 2003 and 2006, and then increased further to 50% in 2007/2008. There was no change thereafter. Intraperitoneal chemotherapy resulted in a significantly improved overall survival (81% v 71% at 3 years; HR 0.68; 95% CI: 0.47 to 0.99), compared with intravenous chemotherapy, but with an increased rate of discontinuation or change of route. (53)

In 2010, surveys were sent to all members of the Society of Gynaecology Oncologists (SGO) and 200 members of American Society of Clinical Oncology (ASCO). They received 209 responses, 24% of SGO and 3% of ASCO. The majority offered intraperitoneal chemotherapy (77%), often 75mg/m² cisplatin. Given the likely bias in those completing the survey, the authors concluded the use of intraperitoneal therapy was low. (54)

The general consensus is that Europe has even poorer uptake of intraperitoneal chemotherapy than the United States though no studies comparing this were identified. (46) Recent National Institute of Clinical Excellence (NICE) guidelines in the United Kingdom in 2011 state that intraperitoneal chemotherapy should not be offered to patients outwith a clinical trial setting. (55) Review articles, written by oncologists based on Italy and based in Germany, also did not support its routine use. (56) (57)

Conclusions:

Intraperitoneal chemotherapy remains an enigma. Adequately powered phase III studies that used cisplatin at a dose of 100mg/m² were largely positive and one of these (GOG-172) demonstrated a 16-month improvement in overall survival which is amongst the most impressive results ever seen in ovarian cancer first line trials. However, many of these trials can be criticised for not comparing equivalent chemotherapy dose intensities in the IP and IV arms. In addition, the IP arms of the largest studies were often less tolerable (most notably in GOG172). A suitable and effective dose of IP carboplatin has not yet been identified, although the regime used in the OV21/PETROC study was equally tolerable to the IV arm and there was a suggestion of activity for this regime.

Current priority areas for first line clinical trials are focussed around novel therapies such as PARP inhibitors, antiangiogenics, immune checkpoint inhibitors and combinations of these agents. As such, there is little appetite at present for academic studies of cytotoxic route of delivery or scheduling. However, the possibility remains that a major opportunity for improving outcome is being missed. The basic immunohistological analysis suggesting patients in GOG-172 who had loss of BRCA1 protein particularly benefited from IP chemotherapy makes biological sense because loss of BRCA1, BRCA2 or other proteins involved in homologous recombination repair is known to confer platinum sensitivity. It is very possible that it is exactly these patients who benefit from the increased exposure to platinum achieved by the IP route of administration. Gene sequence analysis on retrospective material from previous IP studies or prospective recruitment into randomised IP studies based upon loss of homologous recombination repair genes is required in order to more fully explore this possibility.

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